PATENT COOPERATION TREATY

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NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 19 May 2000 (19.05.00)	
International application No. PCT/US99/18618	**Applicant's or agent's file reference** HT-109PCT
International filing date (day/month/year) 23 August 1999 (23.08.99)	**Priority date** (day/month/year) 24 August 1998 (24.08.98)
Applicant EDEN, Ruth, F.	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

24 March 2000 (24.03.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

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PATENT COOPERATION TREATY

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RECD 01 AUG 2000

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

WIPO PC

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference HT-109PCT	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/US99/18618	International filing date *(day/month/year)* 23 AUGUST 1999	Priority date *(day/month/year)* 24 AUGUST 1998
International Patent Classification (IPC) or national classification and IPC IPC(7): B01J 8/18; F27B 15/00, 15/08; C08F and US Cl.: 422/99, 139, 140, 135, 143, 147, 141		
Applicant EDEN, RUTH F.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 3 sheets.

   [✓] This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority. (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 1 sheets.

3. This report contains indications relating to the following items:

   I [X] Basis of the report

   II [ ] Priority

   III [ ] Non-establishment of report with regard to novelty, inventive step or industrial applicability

   IV [ ] Lack of unity of invention

   V [X] Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

   VI [ ] Certain documents cited

   VII [ ] Certain defects in the international application

   VIII [ ] Certain observations on the international application

Date of submission of the demand 24 MARCH 2000	Date of completion of this report 26 JUNE 2000
Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer BAO-THUY L. NGUYEN Telephone No. (703) 308-0196

Form PCT/IPEA/409 (cover sheet) (July 1998)*

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US99/18618

I. Basis of the report

1. With regard to the **elements** of the international application:*

☐ the international application as originally filed

☒ the description:
pages 1-6 , as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of _____

☒ the claims:
pages 7 , as originally filed
pages NONE , as amended (together with any statement) under Article 19
pages 7a , filed with the demand
pages NONE , filed with the letter of _____

☒ the drawings:
pages NONE , as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of _____

☒ the sequence listing part of the description:
pages NONE , as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of _____

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☐ contained in the international application in printed form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the writen sequence listing has been furnished.

4. ☒ The amendments have resulted in the cancellation of:

☒ the description, pages NONE

☒ the claims, Nos. NONE

☒ the drawings, sheets/~~fig~~ NONE

5. ☐ This report has been drawn as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

** Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

***Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US99/18618

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. statement

Novelty (N)	Claims	1-13	YES
	Claims	NONE	NO
Inventive Step (IS)	Claims	1-13	YES
	Claims	NONE	NO
Industrial Applicability (IA)	Claims	1-13	YES
	Claims	NONE	NO

2. citations and explanations (Rule 70.7)

Claims 1-13 meet the criteria set out in PCT Article 33(2)-(4), because the prior art does not teach or fairly suggest a device for separating target microorganism from a suspension containing mixed group of microorganisms using a device comprising an enclosure made of grid material enclosing a plurality of beads coated with at least one antibody material to capture the target microorganism. Which device further comprising means to agitate said enclosure. Although Lewis et al and Yang et al teach a centrifugal fibrous-bed bioreactor comprising cells immobilized in a spiral wound fibrous matrix packed in the bioreactor which may be used for separating target material, these references fail to teach the use of beads coated with antibodies.

---------- NEW CITATIONS ----------

LEWIS et al. Continuous Propionic Acid Fermentation by Immobilized *Propionibacterium acidipropionici* in a Novel Packed-Bed Bioreactor. Biotechnology and Bioengineering. 05 August 1992, Vol. 40, No. 4, pages 465-474.

YANG et al. Kinetics and Stability of GM-CSF Production by recombinant Yeast Cells Immobilized in a Fibrous-Bed Bioreactor. Biotechnol. Prog. 1996, Vol. 12, No. 4, pages 449-456.

YANG et al. Xanthan Gum Fermentation by *Xanthomonas campestris* immobilized in a novel centrifugal fibrous-bed bioreactor. Biotechnol. Prog. 1996, Vol. 12, No. 5, pages 630-637.

8. The method of claim 7 wherein the time period of agitation is at least 30 minutes.

9. The method of claim 7 wherein the time period of agitation extends for several hours.

10. The method of claim 5 including the addition of at least one detergent to the suspension to decrease adsorption of non-specifically bound cells.

11. The method of claim 5 including the subsequent step of immersing the enclosure and beads in a new growth broth.

12. The method of claim 11 including the addition of an indicator material to the new growth broth.

13. The method of claim 5 including the subsequent step of separating the beads from the enclosure followed by at least one test to reveal the microorganisms of interest.

(JMD\Eden - p.7a to Pat. Applic.)

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : B01J 8/18, F27B 15/00, 15/08 — A1

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60/097,627 24 August 1998 (24.08.98) US

(71)(72) Applicant and Inventor: EDEN, Ruth, F. [US/US]; 2765 Ember Way, Ann Arbor, MI 48104 (US).

(74) Agent: DEIMEN, James, M.; Suite 300, 320 N. Main Street, Ann Arbor, MI 48104–1192 (US).

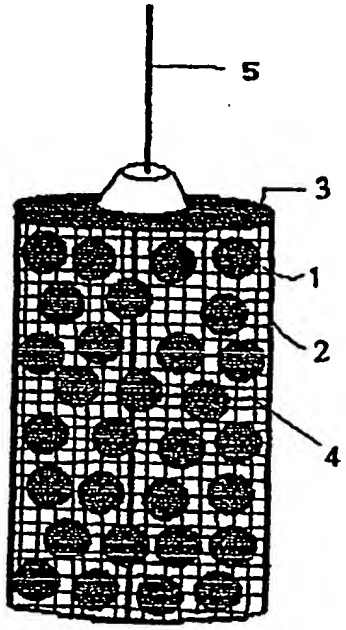
(81) Designated States: AL, AM, AU, AZ, BA, BG, BR, BY, CA, CN, CZ, EE, GE, HR, HU, ID, IL, IN, IS, JP, KG, KR, KZ, LK, LT, LV, MD, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, TR, UA, US, UZ, VN, YU, ZA, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.

(54) Title: METHOD AND DEVICE FOR CONCENTRATING SELECTED GROUPS OF MICROORGANISMS

(57) Abstract

A method and device are described to concentrate target organisms from a mixture of organisms. Beads (1) made of material such as nylon, polystyrene or glass are coated with antibodies of specific microorganisms. The beads (1) are contained in an enclosure (2) surrounded by grid material (4). The pore size of the grid is smaller than the size of the beads, to assure that the beads stay within the grid material and larger than the size of the microorganisms to allow the interaction of the microorganisms with the beads. A rod (5) is attached to the upper part of the enclosure (2) allowing the agitation of the device inside he growth medium containing the target organisms.



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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/18618

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :B01J 8/18; F27B 15/00, 15/08

US CL :422/99, 139, 140, 135, 143, 147, 141

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 422/99, 139, 140, 135, 143, 147, 141

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS, STN

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 3,840,345 A (ANDRE et al) 08 October 1974, see entire document.	1-7
Y	US 4,931,401 A (SAFI) 05 June 1990, see entire document.	1-7
Y	US 5,009,852 A (KITA et al) 23 April 1991, see entire document.	1-7
Y	US 5,186,824 A (ANDERSON et al) 16 February 1993, see entire document.	1-7
A	US 5,776,710 A (LEVINE et al) 07 July 1998, see entire document.	1-7

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search

18 NOVEMBER 1999

Date of mailing of the international search report

30 NOV 1999

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Form PCT/ISA/210 (second sheet)(July 1992)*

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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B01J 8/18, F27B 15/00, 15/08

A1

(11) International Publication Number: **WO 00/10702**

(43) International Publication Date: 2 March 2000 (02.03.00)

(21) International Application Number: PCT/US99/18618

(22) International Filing Date: 23 August 1999 (23.08.99)

(30) Priority Data:
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(71)(72) Applicant and Inventor: EDEN, Ruth, F. [US/US]; 2765 Ember Way, Ann Arbor, MI 48104 (US).

(74) Agent: DEIMEN, James, M.; Suite 300, 320 N. Main Street, Ann Arbor, MI 48104–1192 (US).

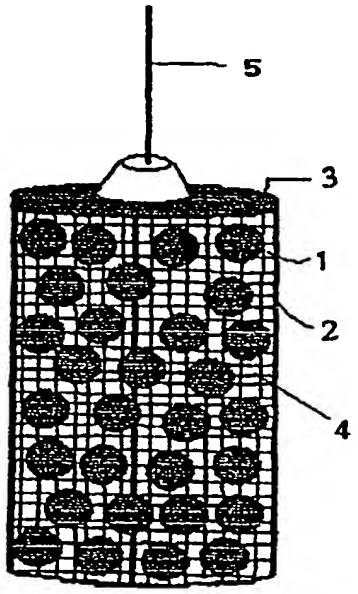
(81) Designated States: AL, AM, AU, AZ, BA, BG, BR, BY, CA, CN, CZ, EE, GE, HR, HU, ID, IL, IN, IS, JP, KG, KR, KZ, LK, LT, LV, MD, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, TR, UA, US, UZ, VN, YU, ZA, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.

(54) Title: METHOD AND DEVICE FOR CONCENTRATING SELECTED GROUPS OF MICROORGANISMS

(57) Abstract

A method and device are described to concentrate target organisms from a mixture of organisms. Beads (1) made of material such as nylon, polystyrene or glass are coated with antibodies of specific microorganisms. The beads (1) are contained in an enclosure (2) surrounded by grid material (4). The pore size of the grid is smaller than the size of the beads, to assure that the beads stay within the grid material and larger than the size of the microorganisms to allow the interaction of the microorganisms with the beads. A rod (5) is attached to the upper part of the enclosure (2) allowing the agitation of the device inside he growth medium containing the target organisms.



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Method and Device for Concentrating Selected Groups of Microorganisms

Background -- Field of Invention.

This application is based on provisional patent application Serial No. 60/097,627, filed August 24, 1998.

The present invention relates to products and processes used for the detection of microbes in a sample. More specifically, the present invention provides a method and device for aiding in the detection of the presence of specific microbial contamination in food samples, clinical specimens and other products.

Background -- Prior Art.

It is necessary to test various substances, such as foods, beverages, pharmaceuticals, cosmetics, water, and body fluids for microbial contamination, especially with certain pathogenic bacteria. Recent outbreaks of foodborne illness, implicating a variety of foods contaminated with pathogenic bacteria, such as *E. coli* 0157:H7, *Salmonella, Listeria, Campylobacter jejuni*, and *Cyclospora*, have underscored the need for rapid methods for microbiological analysis. Microbiological analysis is critical for assessment of safety and quality, to determine efficiency of manufacturing, and conformance with regulations.

The increased scope, significance, and need for microbiological testing served to reveal the limitations and drawbacks of conventional methods. Classical methods for determining the presence of pathogenic bacteria in samples are taking typically several days to perform. It is desired to provide rapid detection of especially pathogenic bacteria causing illnesses.

Since the desired sensitivity for most assays for pathogenic bacteria is less than one such organism in 25 grams of product, most testing methods rely on an initial enrichment step. The indigenous microflora that is usually present in many foods at high levels often interferes with the selective isolation and identification of pathogenic bacteria. Food processing such as heating, cooling, drying,

freezing, addition of preservatives and other causes can sub-lethally injure bacterial cells. These injured cells are extremely sensitive to the ingredients used in selective microbiological media. Therefore, in many assays the process starts with pre-enrichment, in which the sample is incubated in a nutritious, non-selective medium to allow the resuscitation of injured or stressed bacteria. This step is followed by a selective enrichment step where the bacteria of interest are allowed to grow while the indigenous microflora is suppressed. The enrichment procedure is followed either by conventional plating methodology or a variety of more modern and rapid methods such as DNA amplification or immunoassay.

It is therefore desired to separate at an early stage the target organisms from the other flora present in the product. One such approach is the utilization of the immuno-magnetic separation technique, involving the utilization of immuno-magnetic particles specific for the target organisms. Magnetic beads with antibodies affixed to their surfaces are mixed with the sample containing the target organism. This organism will bind to the bead surfaces via the antibodies. The organism-bead complex is pulled out of the solution by a magnet, to concentrate the microorganisms.

U.S. patent 4,230,685 describes magnetically responsive microspheres having protein A associated with the outer surface. The microspheres are reacted with antibodies selective to cells, bacteria or viruses to be separated from a mixed population. The microorganism will attach to the antibody and thereby to the microspheres, and the microspheres are then used in a magnetic separation procedure. The preferred microspheres are prepared from a mixture of albumin, Protein A, and magnetic particles. The microspheres are prepared so that the Protein A is present in the exterior surface of the antibody binding. U.S. patent 4,695,393 describes a process for the preparation of such magnetic beads, which can be used in separation of microorganisms.

U.S. patents 5,491,068 and 5,695,946 describe a method characterized by antibody capture of the organism of interest by the application of specialized magnetic beads. It entails the incubation of the capture cells to form colonies; removal of material from the colonies with colony lift membrane; and detection of the colony material on the membrane sheet by the use of labeled antibodies, PCR or nucleic acid probes. The main problem with this method is the low

sensitivity of one organism per gram. This low sensitivity is inherent in the methodology and is 50-100 fold lower than the desired sensitivity for most food pathogens.

U.S. patent 4,677,055 describes a process for concentrating bacteria utilizing magnetic gel to which anti-specific antigenic determinant antibodies are coupled. It involves the steps of obtaining medium containing the organisms possessing specific antigenic determinants and bringing them in contact with particles of the magnetic gel. This step is followed by the separation of the gel from the medium by magnetic means and inoculation into new medium.

In general there are a number of problems associated with magnetic beads. One such problem results from the small size of such beads (3-10 μm) and the large volume of the medium (250-3,000 ml). As a result it is impossible to remove the magnetic beads from such a large volume. Therefore, many procedures either use a lower sample volume (thereby reducing the sensitivity of the assay) or allow some time (8-18 hours) of pre-enrichment followed by the removal of 1-5 ml of solution for concentration of the target organisms. Another problem associated with the magnetic beads is the fact that they get coated with fat and proteins making it difficult to be collected with a magnet. The process of separating the beads from the medium and washing the unattached bacteria is labor intensive, and creates a contamination hazard of both laboratory surfaces and the beads.

Objects and Advantages.

It is, therefore, an object of the invention to provide a method and device that can be utilized with a large volume of media, to concentrate a target organism. It is another object of the invention to provide a method that is less labor intensive, more rapid and will lend itself to automation.

Still further objects and advantages will become apparent from a consideration of the ensuing description and accompanying drawings.

Brief Description of the Drawings.

Fig. 1 shows a side view of the preferred device utilized to concentrate target organisms.

Fig. 2 shows a side view of another design of the device utilized to concentrate target organisms.

Preferred Embodiment -- Description.

Figure 1 shows the preferred embodiment of a device for the separation of the target organisms from a suspension containing a mixture of organisms. Beads 1 are made of materials such as nylon, polystyrene or glass. The beads are coated with antibodies to specific microorganisms such as *Salmonella, E. coli* 0157:H7 and *Listeria.* A cylindrical enclosure 2 is designed to contain the beads. The enclosure is constructed from a frame 3 supporting a grid 4 covering the frame. The grid's pore size is smaller than the size of the beads to assure that the beads stay within the enclosure 2. However, the pore size is large enough to allow bacteria to freely pass into the enclosure. A rod 5 is attached to the upper part of the enclosure. The rod 5 allows the enclosure 2 to move in the solution and for subsequent removal of the device from the solution.

Figure 2 shows a different design of the device. The beads 11 coated with antibodies are contained in the enclosure 12 made of a grid 13, shaped like a tea bag. A non-wicking string 14 is attached to the upper part of the enclosure 12 allowing movement of the enclosure 12 in the solution, while disallowing the solution containing bacteria to wick up the string. The grid's 13 pore size is smaller than the size of the beads to assure that the beads stay within the enclosure. However, the pore size is large enough to allow bacteria to freely pass into the enclosure.

The food sample to be tested for the presence of the target organism is mixed with the appropriate pre-enrichment broth. The pre-enrichment broth is incubated at an appropriate temperature. Upon the beginning of the incubation period, or alternatively after several hours of incubation, the enclosure 2 is immersed into the broth containing the sample thereby exposing the beads having immobilized thereon monoclonal or polyclonal antibodies to the selected bacteria of interest. This is accomplished by lowering the device 2 into the solution and agitating it for at least 30 minutes and up to several hours. This step allows cell capture by the beads, and the creation of bead-target microbial cell complexes. The next step involves the separation of the beads with the bound target cells from

the suspension containing the food particles and other mixed flora. This is accomplished by pulling the whole device out of the solution, using the rod 5. The device is subsequently washed several times in sterile saline or buffer solution. The washing solution is changed after each wash to remove non-bound organisms. Addition of detergents such as Tween-20 (0.51-0.1 % w/v) or protamine to the incubation broth mixture usually decreases the non-specific adsorption. Tween-20 can be also used in the washing procedure to remove non-specifically bound cells. After the wash step a number of methods can be utilized to detect the presence of the target organism.

Several detection procedures can be used in conjunction with the current invention to detect the presence of the microorganism of interest. For example, the device can be inserted into a new growth broth that includes a dye indicator and the changes in the dye characteristics can be utilized to determine presence or absence of the target organism. The microorganisms do not need to be detached from the beads since attachment to the beads has no effect on their growth. Therefore cells can continue to multiply in the appropriate medium. Alternatively the beads can be removed from the enclosure and inoculated onto the surface of appropriate selective or differential agar. Another approach is to utilize an immunoassay. Most immunoassays require 10^3-10^5 cells ml^{-1}, therefore the beads should contain enough cells to perform a direct immunoassay. Similarly, this method can be combined with DNA hybridization and amplification techniques such as PCR.

As can be seen from the above disclosure, the method of the invention is particularly characterized by the use of immunological beads contained in an enclosure to select out target microorganisms from the sample. The beads must be capable of effectively capturing the target microorganisms from the test sample, while not capturing significant numbers of other organisms that might be present at much higher numbers. However, the antibody used need not be totally specific to the target organism since an additional selection step is available at the end of the assay. The antibodies must be oriented with their binding sites outward to allow contact between the binding portion of the antibody and the target organism. The size of the beads must be larger than the size of the microorganism, to remain contained in the enclosure, while allowing the target

organism to enter the enclosure and attach to the beads. The contact time between the beads and the target organism must be long enough to allow strong interaction. Several hours of interaction was found to yield the best results, i.e. the creation of strong interactions to produce high capture efficiency. After the completion of the incubation step the beads are removed from the solution, by the removal of the enclosure in which they are contained. The enclosure and the beads are washed several times, and the beads are transferred into the detection system.

Conclusions, Ramifications, and Scope.

Accordingly, it can be seen that the new method and device can be utilized with a large volume of media, to concentrate a target organism, without the need to utilize only a portion of the pre-enrichment broth or a small volume of enrichment broth as required for magnetic beads. The invention provides a method and device that is less labor intensive, more rapid and lends itself to automation. Many different designs, for containing the beads during the various steps of the assay, can be utilized.

Obviously, many modifications and variations of the present invention are possible in light of the above techniques. Although the description above contains many specificities, these should not be construed as limiting the scope of the invention but as merely providing illustrations of some of the presently preferred embodiments of this invention. The invention may be practiced otherwise than as specifically described.

What is claimed is:

1. A device for separating specific target microorganisms from suspension containing mixed groups of microorganisms, comprising:

a plurality of beads coated with at least one antibody material to capture the target microorganisms; and

an enclosure made of a grid material enclosing said beads, with a pore size smaller than the size of said beads and larger than the size of the microorganisms.

2. The device of claim 1 wherein said beads are made of resinous material.

3. The device of claim 1 wherein said beads are made of non resinous material.

4. The device of claim 1 further comprising means to agitate said enclosure in the suspension.

5. A method of separating target microorganisms from a suspension containing mixed groups of microorganisms, comprising:

immersing a plurality of beads coated with at least one antibody material into the suspension, said beads being held by an enclosure made of a grid with a pore size smaller than the size of said beads and larger than the size of the microorganisms, thereby allowing the capture of the target microorganisms by said beads; and

washing said beads to remove organisms not bounded to said beads, after pulling said enclosure from the suspension.

6. The method of claim 5 wherein at least one detergent is applied in said washing.

7. The method of claim 5 further comprising agitation of said enclosure holding said beads in the suspension.

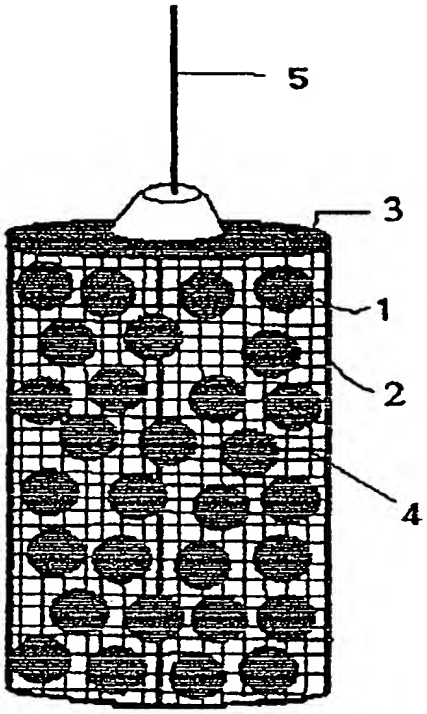

Fig. 1

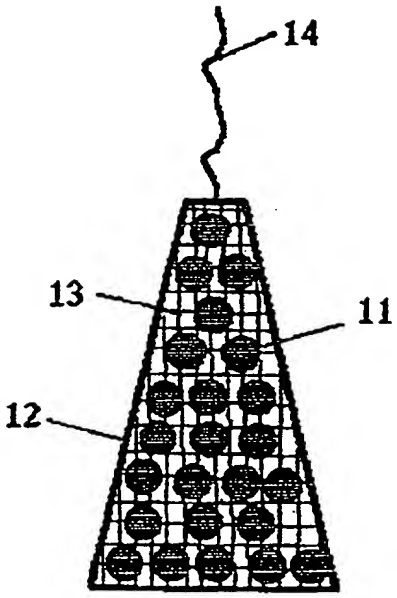

Fig. 2

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/18618

A. CLASSIFICATION OF SUBJECT MATTER
IPC(6) :B01J 8/18; F27B 15/00, 15/08
US CL :422/99, 139, 140, 135, 143, 147, 141
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols)
U.S. : 422/99, 139, 140, 135, 143, 147, 141

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
APS, STN

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 3,840,345 A (ANDRE et al) 08 October 1974, see entire document.	1-7
Y	US 4,931,401 A (SAFI) 05 June 1990, see entire document.	1-7
Y	US 5,009,852 A (KITA et al) 23 April 1991, see entire document.	1-7
Y	US 5,186,824 A (ANDERSON et al) 16 February 1993, see entire document.	1-7
A	US 5,776,710 A (LEVINE et al) 07 July 1998, see entire document.	1-7

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search
18 NOVEMBER 1999

Date of mailing of the international search report
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